Remarks

Claims 1 - 29 are pending in the application, and are subject to a restriction requirement.

Response to Restriction Requirement

Applicants elect, with traverse, the claims of Group IV (claims 11-13 and 15-16, drawn to a method comprising determining the level of activated STAT-3 protein in a patient sample). In the event that no generic claim is ultimately found allowable, Applicants elect the determination of metastatic potential in breast cancer as the relevant species.

Examiner alleges that Groups I - VIII, as outlined on pgs. 2 - 4 of the Detailed Action, are distinct inventions because "they differ in . . . objective, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success." Applicants respectfully disagree.

Restriction is proper only if the pending claims represent independent or distinct inventions, *and* there is a serious burden in searching and examining the entire application. MPEP §803. Here, Examiner cannot show that Groups I - IV represent independent or distinct inventions, or that there is a serious burden on searching and examining these claim groups in one application. Likewise, Groups V - VIII are not independent and distinct inventions, nor is there a serious burden in examining these claim groups together. Thus, to the extent discussed below, the restriction requirement is improper and should be withdrawn.

Examiner has Mis-Characterized the Claims in Groups I Through IV

On pgs. 2 - 3 of the Detailed Action, Examiner has characterized the claims in Groups I - IV by the process step through which the claimed result is achieved. For example, claim groups I and II are identified as being "drawn to expressional analysis of c-fyn" by determining relative levels of RNA transcripts and protein levels, respectively. Likewise, the claims in Groups III and IV are identified as being "drawn to a method of determining the relative level of activated STAT-3 protein" by measuring STAT-3 binding activity or phosphorylation, respectively.

The method claims in these claim groups are actually drawn to methods of predicting the clinical outcome of a cancer, as measured by the cancer's metastatic potential and grade, or by the patient's prognosis. One predicts the clinical outcome of a cancer in the claimed methods by measuring either c-fyn expression or the level of activated STAT-3 protein in the patient's cancer cells.

Claim Groups I Through IV and V Through VIII Are Not Independent

Independent inventions are unconnected in design, operation or effect. MPEP §802.01. As discussed above, there is a clearly disclosed relationship between the methods recited in Groups I - IV; *i.e.*, that the claimed methods all relate to predicting the clinical outcome of a cancer. See, for example, the passage under the heading "Cancer Prognosis" on pgs. 3 - 4 of the specification, which reads:

> The ability to identify cancer patients with more aggressive diseases is crucial to planning adequate treatment. Selecting an appropriate course of therapy requires an accurate determination of the cancer's malignant potential. With this purpose in mind, several pathologic tumor features have been considered so far, including histologic type, grade of differentiation, depth of invasion, and extent of lymph nodal metastases . . . There is great need for a simple laboratory test which is a consistent predictor of clinical outcome in cancer.

The "simple laboratory test" comprises assaying for molecular markers of cancer severity as disclosed in the specification, such as c-fyn expression or activated STAT-3 protein. These molecular markers may be detected by different assays, for example by detecting c-fyn expression at the protein or RNA level, or by detecting activated STAT-3 directly as the phospho-protein or functionally through its DNA binding activity. Far from being different inventions, these assays are merely separate facets of the same general concept; *i.e.*, detecting the molecular marker. The various claims of Groups I - IV are thus related in operation and effect, and cannot be independent.

The claims in Groups V - VIII are likewise related as methods for identifying compounds that inhibit cell proliferation, and are therefore not independent. Here, different assays are used to detect Src-kinase activity in response to a particular test compound, which

is then used to assess extent of cell proliferation. The Src-kinase activity may be measured directly by detecting levels of STAT-3 or STAT-5 phospho-protein, or indirectly by measuring phosphorylated STAT-3 or STAT-5 DNA binding activity, in various experimental systems. Again, these assays represent alternative ways of achieving the same result; *i.e.*, determining the effect of a test compound on cell proliferation by measuring Src-kinase activity. The various claims of Groups V - VIII are thus also related in operation and effect, and cannot be independent.

Claim Groups I Through IV and V Through VII Are Not Distinct

Inventions are distinct only if they are 1) classified separately, 2) have acquired separate status in the art when classified together, *or* 3) require a different field of search (*i.e.*, it is necessary to search for one invention in places where no pertinent art exists for the others). MPEP §808.02. Here, Examiner insists that Groups I - VIII "have acquired separate status in the art as shown by their different classification." (see pg. 4 of the Detailed Action).

With regard to Groups I through IV, the groups are not classified separately under §808.02(A), as Examiner has put each group in the identical class (435). Moreover, both Groups I and III are classified in subclass 6, and Groups II and IV are classified in subclasses 7.1 and 7.23, which are closely related to each other and to subclass 6[1].

Groups I through IV also do not represent "separate inventive effort" under §808.02(B), as they all relate to the same objective of predicting clinical outcome in a cancer by detecting specific molecular markers. The discussion above with respect to the recitation of alternative c-fyn and activated STAT-3 assays, each of which achieves the same result, applies equally here.

Finally, Groups I through IV do not require a different field of search under §808.02(C), because they all carry the identical classification and have identical or closely related subclassifications. It is unlikely that a search of one claim group would reveal no art that is pertinent to the others.

[1] See the Manual of Patent Classification under class 435, which relates the subclasses as follows: Subclass 6 and 7.1 are both indented under subclass 4, and subclass 7.23 is subsumed into subclass 7.21, which itself relates back to subclass 7.1.

Thus, Groups I - IV fail to satisfy any of the criteria set forth in MPEP §808.02, and thus are not distinct.

Groups V - VIII also do not satisfy the criteria set forth in MPEP §808.02, and thus do not represent distinct inventions: These claim groups are not classified separately under §808.02(A), as Examiner has again put each group in class 435. Also, Groups V and VII have been classified in subclass 4, and Groups VI and VIII have been classified in closely related subclass 6[2]. These claim groups also do not represent "separate inventive effort" under §808.02(B), as all relate to methods for identifying compounds which inhibit cell proliferation via measuring Src kinase inhibition. The discussion above with respect to the recitation of alternative Src kinase activity assays, all of which achieve the same result, applies equally here. Finally, these claim groups do not require a different field of search under §808.02(C), because they carry the identical classification and have identical or closely related subclassifications.

Restriction Is Improper for Groups I Through IV and for Groups V Through VIII

As shown above, Groups I - VI and V - VIII, respectively, are not independent and are not distinct. According to MPEP §§806 and 806.05, if inventions are related but not distinct, restriction is "never proper."

There Is No Serious Burden In Searching Claim Groups I Through IV

Even assuming *arguendo* that Groups I - IV or Groups V - VIII, respectively, represent independent or distinct inventions, restriction is not proper because there is no serious burden on Examiner in searching all claim groups.

According to MPEP §803 (emphasis added), "a serious burden . . . may be prima facie shown if the examiner shows *by appropriate explanation* either separate classification, separate status in the art, or a different field of search as defined in MPEP §808.02." Examiner has given no explanation at all to support a contention that searching either Groups I - IV together, or Groups V - VIII together, pose a serious burden. Moreover, as discussed above, Groups I - IV and Groups V - VIII fail to satisfy any of the criteria set forth

[2] Subclass 6 is indented under subclass 4; see n1.

in MPEP §808.02. Thus, there can be no serious burden in searching either Groups I through IV or Groups V through VIII in the same application.

Conclusion

Claim Groups I through IV or Groups V through VIII represent, respectively, non-independent and non-distinct inventions that do not present a serious search burden for Examiner. Withdrawal of the restriction requirement with respect to Groups I through IV, and with respect to Groups V through VIII, is therefore proper. In light of the election of Group IV above, Applicants respectfully request that the claims of Groups I - IV be recombined and examined in the present application.

Applicants remind Examiner that MPEP §803 places the burden squarely on the examiner to "provide reasons and/or examples to support conclusions" presented in a restriction requirement. See also MPEP §808.02(B). Thus, if Examiner maintains any or all of the present the restriction requirement, Applicants respectfully request that Examiner clearly articulate reasons and/or provide examples and evidence in support of his position.

Respectfully submitted,
E. PREMKUMAR REDDY et al.

BY _____
DANIEL A. MONACO
Registration No. 30,480
DRINKER, BIDDLE & REATH, LLP.
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103
(215) 988-3312 ph.
(215) 988-2757 fax
Attorney for Applicants